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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TIDWELL, JUDY LILLE	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,724	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	Judy Lille Tidwell, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/21/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,71,76-82,84,85,91-112,115 and 121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,71,76,77,79-82,84,85,91-107,109-112,115 and 121* is/are rejected.

7)☒ Claim(s) *78, 108* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Srivastava

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 July 2005, and 21 November has been entered. It is noted that applicant has amended claims 96-98 and 100 to clarify that "the compound is" an alpha (2) macroglobulin receptor fragment. Claims 112 and 115 have been amended to correct dependencies to delete claim redundancies. Claims 94, 96-100, 11, 112, and 115 have been amended to recite "alpha (2) macroglobulin" rather than "α2M". Claims 113, 114, and 116-120 have been canceled without prejudice.

Claims 31, 71, 76-82, 84, 85, 91-112, 115, 121, are currently pending and under consideration.

The restriction/election requirement set forth on 09 June 2005 is withdrawn and the search is expanded to other species.

This Office action contains new grounds of rejection.

The text of those sections of Title 35, U.S. Code are not included in this action and can be found in a prior Office action.

Claim Rejections Withdrawn - 35 USC § 112

The rejection of claims 31, 71, 76, 80-82, 84, 85, and 91 under 35 USC § 112, 1st paragraph (from office action on 02/09/2005) as lacking written description is withdrawn in view of the amendments to the claims and the persuasive arguments presented by the applicant.

Claim Rejections Withdrawn - 35 USC § 112

Claims 31, 71, 76-82, 84, 85, and 91-112, 115, and 121 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement is withdrawn (in part?). Applicant's arguments will be addressed in the scope of enablement rejection below.

The Following Are New Grounds of Rejections

Claim Objections

Claims 76, and 84 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The base claims 31 and 71 that the instant claims 76 and 86 depend on are construed using Markush language, i.e. "group consisting of". A Markush group lists specified alternatives in a patent claim, typically in the form: a member selected from the group consisting of A, B, and C. MPEP 2111.03 [R-3] Transitional Phrases. A Markush group by its nature is closed. Thus, the scope of the claimed compound in the base claims are limited to the group consisting of "an antibody, an alpha (2) macroglobulin fragment, and an alpha (2) macroglobulin receptor fragment".

The specification at page 37, lines 8-14 discloses:

> The compounds which may be screened in accordance with the invention include, but are not limited to small molecules, peptides, antibodies and fragments thereof, and other organic compounds (i.e. peptidomimetics) that bind to the ECD of the a2M receptor and either inhibit the activity triggered by the natural ligand (i.e. antagonists) or mimic the activity triggered by the natural ligand (i.e. agonists), as well as small molecules, peptides, antibodies or fragments thereof, and other organic compounds.

Thus, the term "an antagonist" in claim 76, which includes organic compounds, is broader in scope than the scope encompassed by the "compound" in the respective base claims.

Likewise, the term "peptide" in claim 84 is broader than the scope of the compound limited by the Markush members of the base claims.

Claim Rejections - 35 USC § 112

Claims 31, 71, 76, 77, 79-82, 84, 85, and 91-107, 109-112, 115, and 121 (all claims except claim 78 and 108 drawn to an antibody specific for the α2M receptor) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting an immune response with an antibody specific for the α2M receptor, does not reasonably provide enablement for inhibiting an immune response with any of the other recited products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that the disclosure of the instant application enables methods of inhibiting an immune response comprising administering to a human in need thereof a purified compound which interferes with the interaction of a heat shock protein with the α2MR because the *in vivo* utility is supported by *in vitro* cell-based assays. More specifically, applicant contends that antibodies against α2MR inhibited the re-presentation of heat shock protein peptide complexes in a cell-based assay. Applicant asserts that the inhibition *in vitro* is indicative of *in vivo* success because the assay uses cells involved in immune responses *in vivo*. From this, applicant concludes that it would not be unreasonable to extrapolate *in vitro* cell culture assays to cells *in vivo* because the mechanism of peptide presentation is maintained.

Applicant argues, in view of *In re* Brana, 51 F.3d 1560. 1567 n.19 (Fed. Cir. 1995), that post-filed references provided by applicant demonstrate enablement and a correlation between the ability of an anti-CD91 antibody to block re-presentation of a heat shock protein peptide complex *in vitro* with inhibition of the protective immunity otherwise elicited by the heat shock protein peptide complex *in vivo*. Applicant argues that Binder et al. (2004, *PNAS* 101:6128-6133) teach the *in vivo* effects of an α2M receptor antibody (anti-CD-91) on the re-presentation of the gp96-ova peptide complex. Applicant also argues that Binder et al. (2002, *Cancer Immunity* 2:16-24) teach that the administration of anti-CD91 with a gp96-peptide complex did not inhibit the growth of Meth A fibrosacrcomas and that this provides evidence of inhibiting an immune response to the tumor.

Applicant's arguments have been fully considered but not found persuasive because applicant's arguments using the two post-filing references mentioned above are not commensurate in scope of the claims. The breadth of the claims are broader than the antibody (anti-CD91) that applicant now argues with the post-filed references discussed above. The claimed invention is drawn to methods using products, such as any antibody, α2M fragments, or α2M receptor fragments, other than the enabling antibody (anti-CD91).

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CAFC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex pade Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404).

Nature of invention

The claims are drawn to a method for inhibiting an immune response comprising administering to a human in need thereof a purified compound that binds to the α2M receptor or interferes with the interaction of a heat shock protein with the α2M receptor. The invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Breadth of the claims

The breadth of the claims are broad, including any antibody that interferes with the interaction of a heat shock protein with the α2M receptor, an α2M fragment (SEQ ID NO: 9) and other fragments that bind to the α2M receptor or interfere with the interaction of a heat shock protein with the α2M receptor, or an α2M receptor fragment (SEQ ID NO: 21) and other fragments that bind to the α2M receptor or interfere with the interaction of a heat shock protein with the α2M receptor and encompass methods for inhibiting an immune response.

Quantity of experimentation necessary

There is a significant variability in the quantity of experimentation involving methods for inhibiting an immune response in a human with a purified compound that binds to the α2M receptor or interferes with the interaction of a heat shock protein with the α2M receptor. Binder et al. (2002, 2004) teach the experimentation that enables the use of one antibody that binds to the α2M receptor for inhibiting an immune response is large, even in the case of mice *in vivo*, let alone in a human subject. The quantity of experimentation to enable the methods for inhibiting an immune response in a human (applying the breadth of the claimed products) using all of the claimed products would

require significant study, with many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Predictability or unpredictability of the art and State of the prior art

The art is unpredictable with regard to the amount of undue experimentation needed to demonstrate that a compound, which interferes with the interaction of a heat shock protein with the α2M receptor, can inhibit an immune response in a human by administering said compound. Binder et al. (2002, 2004) teach one example where administration of anti-CD91 inhibited an immune response. However, Binder et al. (2004) consider their results as "suggestive of a role of HSP-CD91 interaction in the human immune system and require further interrogation with more precise experimental strategies" (page 6133, right column, last sentence). Further, Bellone et al. (1999, *Immunology Today* 20:457) summarize the current state of the art of peptide immunotherapy as "...a poor correlation between induction of specific T-cells and the clinical responses".

Presence of working examples

The post-filed references provide data that is limited to one species of antibody (CD-91) that inhibits re-presentation of a heat shock protein peptide complex. The specification provides no working examples for any of the other claimed products for a method of inhibiting an immune response comprising administering to a human.

Amount of direction or guidance presented

The specification contemplates further encompassing methods for modulating the immune response (line 5, page 49) by using compounds that interact with the α2M receptor and its ligand. The specification recites that identified compounds could be useful as therapeutics, such as blocking an immune response to treat autoimmune responses and conditions (lines 20-26, page 49). The specification further contemplates that autoimmune diseases can be treated with the methods of the instant invention by "reducing or eliminating the immune response to the patient's own (self) tissue ..." (lines 17-21, page 65). Finally, the specification provides pharmaceutical preparations and methods of administration (line 15, page 67 – line 24, page 69). However, the specification is silent to any process steps or analysis of how to determine

whether or not and to what extent the administration of said identified compound will inhibit an immune response in a mammal or human.

Relative skill of those in the art

The level of skill in the art is deemed to be low.

Conclusion

Considering the broad scope of the claims in respect to the products being used to accomplish the purpose set forth in the preamble of the claims, and limited guidance as to how to make the products with the recited function other than the antibody in claim 78, and unpredictable state of the art for *in vivo* human treatment, it is concluded that undue experimentation is needed to practice the full scope of the claims.

Claim Rejections - 35 USC § 112

Claims 31, 76, 84, 92, 93, 102, 105, and 121 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).
Claims 31, 71, 76, 84, 92, 93, 102, 105, and 121 are drawn to method using genus of "antibody", "peptide", or "antagonist".

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case where "an antibody" recited in base claims 31 and 71, the Federal Circuit has ruled that "as long as an applicant has disclosed a 'fully characterized antigen's either by its structure, formula, chemical name, or physical properties, or by

depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." Noelle v. Lederman, 69 USPQZd 1508, 1514 (Fed. Cir. 2004). The structure of the antigen(s) the claimed antibody binds to is not in the claims.

As for the claimed "peptide" and "antagonist", there is not even identification of any partial structure, let alone complete structure, in order to have the recited function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Conclusion

Claims 78 and 108 are objected because they depend on the rejected base claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Judy Lille Tidwell, PhD whose telephone number is 571-272-5952. The examiner can normally be reached between 8:00AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU
PATENT EXAMINER

JLT